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## ORIGINAL ARTICLE

# Extra-uterine renal growth in preterm infants: Oligonephropathy and prematurity

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## Abstract

**Background** Nephron number in humans is determined during fetal life. The objective of this study was to investigate the effects of preterm birth on nephron number using renal volume as a surrogate for nephron number.

**Methods** This observational study was conducted over 12 months in a tertiary perinatal center. Preterm babies less than 32 weeks of gestation were recruited and followed until discharge. Term infants were recruited for comparison. The babies underwent renal sonography and renal function measurements at 32 and 38 weeks corrected age. The primary outcome measurement was total kidney volume at 38 weeks and the secondary outcome was estimated glomerular filtration rate (eGFR).

**Results** Forty-four preterm infants and 24 term infants were recruited. At 38 weeks corrected age, premature infants had lower total kidney volume than term infants ( $21.6 \pm 5.7$  vs.  $25.2 \pm 5.7$  ml;  $p=0.02$ ) and a significantly lower eGFR ( $73.6$  [IQR  $68.1$ – $77.6$ ] vs.  $79.3$  [IQR  $72.5$ – $86.6$ ]  $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ;  $p=0.03$ ). There was a significant correlation between total kidney volume and eGFR in premature and term babies.

**Conclusions** Premature infants have smaller kidney volume and likely decreased nephron number and lower estimated glomerulofiltration rate relative to infants born at term.

**Keywords** Glomerulogenesis · Preterm · Oligonephronia · Cystatin C · Kidney volume

## Introduction

The World Health Organization (WHO) estimated that in 2010 14.9 million, or 11.1 % of all births worldwide, were preterm (defined as childbirth occurring at less than 37 completed weeks of gestation) [1, 2]. While there has been a slight decline in the preterm birth rate in the US [3], the survival rate of premature babies in developing countries has improved over time [4, 5], and therefore the number of premature babies surviving to adulthood is anticipated to increase.

Evidence from animal studies [6, 7], human autopsy findings [8, 9], and epidemiology data [10, 11] have indicated that prematurity, independent of birth weight, results in abnormal renal development and predisposes adults to the development of chronic kidney disease (CKD). Nephron number in humans is determined during fetal life, as nephrogenesis is completed between 34 and 36 weeks of gestation [7, 12, 13]. Preterm birth prior to 36 weeks therefore occurs during the process of glomerulogenesis. In adults born prematurely, there is an association between poor maternal health [14] coupled with neonatal interventions and a nephron endowment is far lower than term born peers [15]. Low nephron number triggers a vicious cycle that is associated with glomerular hyperfiltration, glomerular damage, proteinuria, hypertension, and long-term progression to CKD [16, 17]. The only accurate method for determining nephron number is to visually count nephrons after autopsy [9, 12], but this is rarely possible in the clinical setting. Animal studies [18] and autopsy findings from young infants [19] suggest that kidney volume correlates well with total nephron number and could be used as a non-invasive surrogate measurement.

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Antenatal scans have shown that the normal fetal renal parenchyma grows at a constant and linear rate throughout pregnancy [20]. However, there are very limited data on extrauterine renal growth in premature babies, and it is therefore unclear when the defects in nephron number arise in adults born prematurely. In this study, we postulated that premature infants at term corrected age (CA) would have fewer glomeruli and, as a result, smaller kidney volumes than term infants. To test this hypothesis, we analyzed the effect of prematurity on renal volume in a cohort of premature infants admitted to a tertiary perinatal center for treatment.

## Methods

This prospective observational study was performed at the Department of Neonatology, Townsville Hospital, Australia, which is a tertiary perinatal center responsible for a region with more than 10,000 births annually. Approximately 2,000 of these births occur at the hospital itself. Recruitment of babies for this study was limited to babies admitted to the department. The study commenced in August 2010, and the recruitment period lasted for 12 months. Patients were recruited prospectively and data analysis was carried out retrospectively upon completion of the study period. The Townsville Health District Human Research Ethics Committee approved this study, which was conducted in accordance with the tenets of the Declaration of Helsinki. Written parental consent was obtained from parents of all infants who participated in this study.

### Patients

Preterm babies at less than 32 weeks of gestation admitted to the neonatal intensive care unit during the study period were eligible to participate in this study. Patients with congenital abnormalities or syndromes were excluded. Preterm babies were recruited and followed until discharge. Once recruited, the patients underwent a first assessment (renal sonography and renal function measurement) at 32 weeks CA and a second assessment at 38 weeks CA (renal sonography, renal function, and blood pressure measurements). CA for the premature babies was defined as: [CA = age at birth (gestational age in weeks) + postnatal age in weeks] [21]. For example, a premature baby born at 28 weeks of gestation will be 32 weeks CA after 4 weeks of postnatal life and 38 weeks CA after 10 weeks of postnatal life.

Term babies with a birth weight that was appropriate for gestational age (AGA) [22] admitted to the special care nursery during the same study period were also recruited for this study. These infants were admitted for non-life-threatening neonatal problems, such as neonatal jaundice, risk of sepsis,

and transient tachypnea of the newborn (TTN). None of the patients received nephrotoxic medications and none developed acute kidney injury. Term babies with congenital abnormalities or syndromes, infants requiring respiratory care, infants of diabetic mothers, small for gestational age (SGA) and infants whose parents did not provide written consent were excluded from the study. All term infants underwent renal sonography, renal function assessment, and blood pressure measurements within the first week of life. All three measurements were obtained on the same day.

### Anthropometric and blood pressure measurements

All anthropometric and blood pressure measurements were carried out by neonatal nurses. For all newborn premature infants, birth weight was measured using an electronic weighing scale built into the incubator (Giraffe Incubator, General Electrics Healthcare, Laurel, MD, USA). These incubators undergo scheduled maintenance and calibration by biomedical engineers, as determined by the manufacturers.

All other body weight measurements were performed with an electronic infant weighing scale (Seca 727 Electronic baby scale, Seca Deutschland, Hamburg, Germany).

The length measurement (head to toe) was carried out with the infant lying supine and with the body, hips, and knees straightened; measurements were taken twice and then averaged. Mean blood pressures were determined for each infant at 32 and 38 weeks for premature babies and once, neonatally for term infants. The blood pressure was obtained using a non-invasive blood pressure recording system (Dash 4000 Monitor; GE HealthCare, Waukesha, WI, USA). An infant cuff was applied to the right upper arm with the infant calm and lying supine. Three successive BP recordings were taken at 2-min intervals and the mean calculated [23].

### Kidney ultrasonography

All renal ultrasounds were obtained using the Philips IU22 Ultrasound System (Philips Healthcare, Andover, MA, USA) with a compact (small footprint) curved linear 5–8 MHz frequency transducer. To avoid inter-observer bias during scanning and measuring, all ultrasound scans of the kidneys were reported by a single pediatric radiologist, who was blinded to the clinical information. Intra-class coefficient for intra-observer variability was 0.85 (95 % confidence interval 0.73–0.91). Renal length (L), anteroposterior diameter (AP), and transverse diameter (W) were measured for both kidneys. Kidney volume (KV; ml) was calculated according to the following formula:  $KV = (\pi/6 \times L \times W \times AP)$  [24]. The mean volume of the right and left kidneys [(Right KV + Left KV)/2] and total KV (Right KV + Left KV) were also calculated.

## Renal function and GFR calculations

Venous blood was collected through a peripheral venipuncture for serum creatinine and cystatin C (Cys C) measurements from each patient on the same day as the renal sonogram was obtained. Serum Cys C was measured using a commercially available kit according to the manufacturer's instructions (Beckman Coulter, Gentian AS, Moss, Norway). Coefficient of variation for this measurement was 6 %. A creatinine/Cys C-based prediction equation was then used to calculate the estimated glomerular filtration rate (eGFR) as follows:  $\text{eGFR}(\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}) = [507.76 \times e^{0.003 \times \text{height}}] / [\text{CysC}^{0.635} \times \text{SCr}^{0.547}]$  [25].

## Outcome measures

The primary outcome measured in this study was total kidney volume (TKV). The TKV was assessed at 32 weeks CA and 38 weeks CA for premature babies and within the first week of life for term infants. The secondary outcome was a comparison of eGFR.

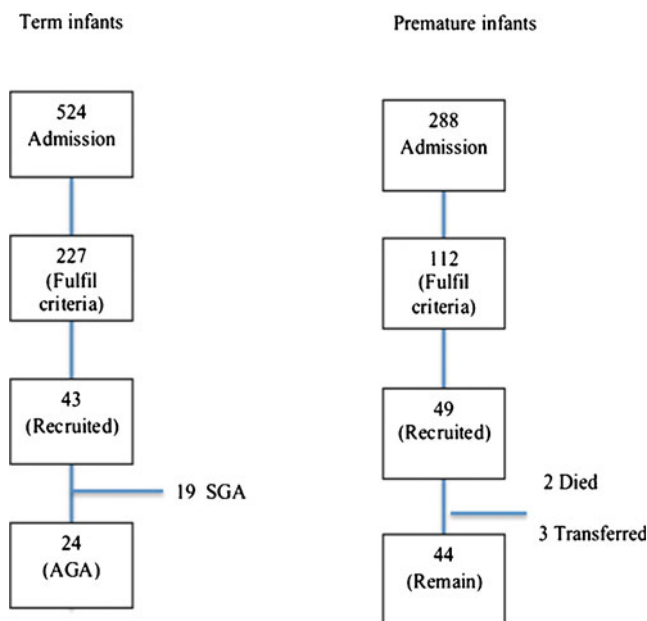
## Statistical methods

Data from a previously published study show that the TKV in term infants is  $9.6 \pm 2.6$  ml [26]. Studies in adults who were born prematurely show that their kidney volume is 15 % lower than that of adults who were born at term [27], thus, for a study with  $\alpha=0.05$  (two-sided) and  $\beta=80$  %, 26 patients were estimated to be needed for each cohort. The normality of the variables was determined by the D'Agostino-Pearson test [28]. The results were expressed as the means  $\pm$  SD for continuous, normally distributed data and as median [IQR] for continuous, non-normally distributed data. Comparisons of means of normally distributed data were made using paired/unpaired *t* tests, and Mann–Whitney or Kruskal–Wallis tests were used for non-normally distributed data. A *p* value  $<0.05$  was considered statistically significant. Statistical analyses were performed using Stata Version 11.0 statistical software (StataCorp, College Station, TX, USA).

## Results

Figure 1 summarizes the number of patients available for recruitment and the actual number recruited. Forty-nine preterm babies were recruited; two babies died, and three were transferred back to regional hospitals preventing assessment and inclusion in the study. None of the patients received nephrotoxic medications and none developed acute kidney injury.

The deceased preterm infants were also small for their gestational age (SGA, birth weight  $<10$ th percentile). Data from 44 preterm babies were used for analysis (18 females,



**Fig. 1** Selection of preterm and term babies for the study. AGA appropriate for gestational age, SGA small for gestational age

26 males). Twenty-four term babies (ten females, 14 males,) with birth weights that were appropriate for gestational age (AGA; weight between 10th–90th percentile) were also recruited. The mean gestational age for premature infants was  $28.0 \pm 2.4$  weeks, with a mean birth weight of  $1,133 \pm 339$  g. The median gestational age for the term babies was 38.7 weeks [IQR 37.1–39.4 weeks], and the mean age at assessment was  $5.0 \pm 2.3$  days.

Table 1 summarizes the clinical data for preterm and term infants. At 38 weeks corrected age (CA), premature infants had smaller total kidney volume (TKV)s than term babies ( $21.6 \pm 5.7$  vs.  $25.2 \pm 5.7$  ml;  $p=0.02$ ) (Fig. 2). They also had smaller body weights compared to term infants ( $2,566 \pm 406$  vs.  $3,416 \pm 433$  g;  $p<0.001$ ). Preterm infants at 38 weeks CA had significantly higher levels of Cys C ( $1.41$  [IQR 1.28–1.58] vs.  $1.18$  [IQR 1.1–1.40] mg/l;  $p=0.03$ ) and a lower eGFR ( $73.6$  [IQR 68.1–77.6] vs.  $79.3$  [IQR 72.5–86.6]  $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$ ;  $p=0.03$ ) compared to term babies. There was no difference in mean blood pressure measurements between the preterm infants at 38 weeks CA and term babies. There were also no significant differences in the mean TKV of male and female preterm infants at either 32 weeks CA ( $15.2 \pm 4.6$  vs.  $13.9 \pm 5.2$  ml;  $p=0.39$ ) or at 38 weeks CA ( $22.1 \pm 5.1$  vs.  $20.9 \pm 6.7$  ml;  $p=0.48$ ). There were no significant differences between right and left kidney volumes in preterm infants at 32 weeks CA ( $7.6 \pm 2.5$  vs.  $7.2 \pm 2.4$  ml;  $p=0.39$ ) and 38 weeks CA ( $11.1 \pm 3.1$  vs.  $10.7 \pm 2.9$  ml;  $p=0.50$ ).

When total kidney volume was corrected for body weight (TKV/BW), a different trend was observed (Fig. 3). At 32 weeks CA, the TKV corrected for body weight was

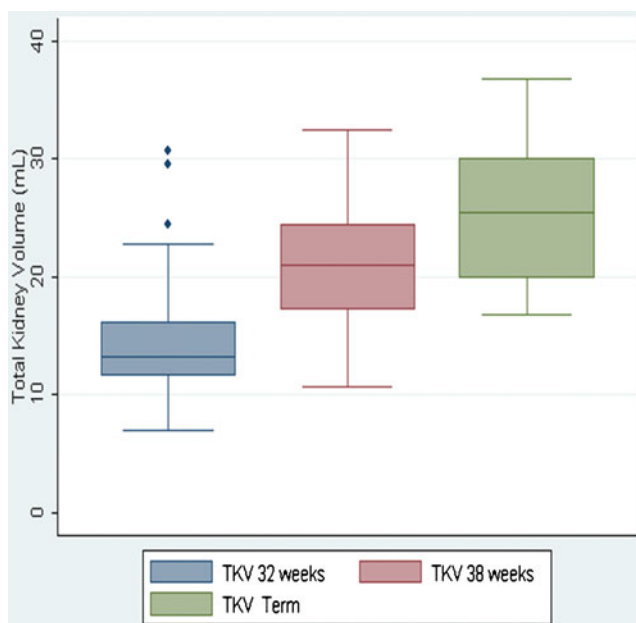
**Table 1** Comparison between term and premature infants

	Preterm infants		Term infants
	1st assessment	2nd assessment	
Number of infants	44	44	24
Gestation (weeks)	32.2 [31.8–32.2]	38.0 [37.7–38.1]	38.7 [37.1–39.4]
Mean weight (g)	1,447±250	2,566±406	3,416±433
Mean length (cm)	38.9±4.0	45.0±3.2	50.1±2.1
Mean blood pressure (mmHg)	41.3±2.1	59.8±10.0	57.9±6.8
eGFR (ml·min <sup>-1</sup> ·1.73 m <sup>-2</sup> )	67.2 [IQR 55.3–79.2]	73.6 [IQR 68.1–77.6]	79.3 [72.5–86.6]
Mean kidney length (cm)	3.6±0.3	4.2±0.3	4.5±0.4
Mean kidney width (cm)	2.0±0.2	2.2±0.2	2.3±0.2
Total kidney Volume (ml)	14.5±4.7	21.6±5.7	25.2±5.7
Serum creatinine (μmol/l)	37.8±9.8	30.6±2.3	37.8±16.5
Cystatin C (mg/l)	1.40 [IQR 1.2–1.6]	1.41 [IQR 1.28–1.58]	1.18 [IQR 1.1–1.40]

eGFR estimated glomerular filtration rate

significantly higher than that at 38 weeks CA ( $10.2\pm2.7$  vs.  $8.5\pm2.2$  mL/kg;  $p<0.001$ ). Premature infants at 38 weeks CA had larger TKV corrected for body weight compared to term infants ( $8.5\pm2.2$  vs.  $7.4\pm1.7$  mL/kg;  $p=0.03$ ).

We carried out a correlation analysis for TKV and eGFR using Spearman's rank correlation coefficient ( $\rho$ ) and found a significant correlation in premature babies at 32 weeks CA [ $\rho=0.35$  (95%CI 0.07–0.58);  $p=0.02$ ], 38 weeks CA [ $\rho=0.41$  (95 % CI 0.12–0.64);  $p=0.01$ ] and in term babies [ $\rho=0.62$  (95 % CI 0.27–0.82);  $p=0.002$ ].

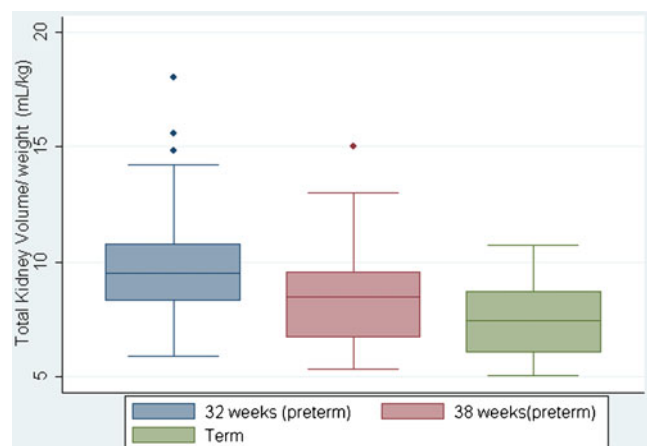


**Fig. 2** Box plot showing difference in total kidney volume between preterm (32 weeks and 38 weeks) and term babies (one-way ANOVA;  $p<0.001$ , degree of freedom=2)

## Discussion

In our cohort, kidney volume was lower in premature infants at term CA than in term infants. Premature babies also had a lower eGFR compared to term infants, which was possibly due to a reduced number of nephrons. We found that total kidney volume had a positive correlation with eGFR in both premature and term babies, which supports the hypothesis that kidney volume in young infants can be used as a surrogate marker of nephron number.

When kidney volume was corrected for body weight, premature infants had larger kidney volumes. The reason and clinical significance (if any) for this finding is not known. However, other investigators have reported similar findings in other studies. Rodriguez et al. carried out one of the earliest renal histopathological studies on a cohort of 56



**Fig. 3** Box plot comparing total kidney volume corrected for body weight in preterm (32 weeks and 38 weeks CA) and term babies (one-way ANOVA;  $p<0.001$ , degree of freedom=2)



extremely premature infants (gestational age between 23 and 30 weeks; birth weight of 1,000 g or less) [9]. Preterm infants were divided into two groups based on the length of survival in the neonatal period (less or more than 40 days). The authors of that study found that glomerulogenesis ceased after 40 days of extra-uterine life and that premature infants who survived longer had significantly larger glomeruli. The investigators also found that premature infants more than 40 days old had greater kidney weights compared to the control group. A more recently published study by Sutherland et al. [8] came to the same conclusion. The investigators in that study reviewed renal histopathological specimens obtained from the kidneys of 28 premature neonates, including six with intrauterine growth restriction (IUGR) who survived between 2 and 68 days in the neonatal period. The investigators found premature infants had a significantly larger kidney weight to body weight ratio compared to the controls.

Kidney volume in premature babies and its relationship to body weight has also been investigated non-invasively. Huang et al. [29] assessed extra-uterine kidney volume development and then compared it to intrauterine growth. Serial kidney ultrasonographs were obtained to measure renal volume in a cohort of 56 premature infants born before 34 weeks of gestation at 14–96 days after birth. The investigators found that the kidney volume/body weight (KV/BW) ratio was significantly higher in premature infants. From our study, we are unable to determine the cause for this decline in KV/BW as shown in Fig. 3. Previously published studies [8, 9] showed kidneys of premature babies to have larger glomeruli but did not ascertain the cause for these phenomena. Perhaps this is due to a compensatory mechanism but more studies are needed to confirm this hypothesis.

In our study, we used CysC to measure eGFR. CysC is a cysteine proteinase inhibitor composed of 122 amino acids and is produced by a housekeeping gene expressed in all nucleated cells at a constant rate and is freely filtered in the glomerulus with no tubular secretion [30]. Moreover, CysC is completely catabolized by the renal tubules; thus, its plasma level is only dependent on GFR [30]. Meta-analyses have shown that CysC is superior to SCr for estimating GFR in children [31, 32]. In neonates, there is no correlation between maternal and neonatal serum CysC levels [33]. CysC measurements do not differ between male and female infants, and most importantly, there are no gestational age-dependent differences in CysC levels [34–36].

There are several limitations to our study. First, only a small proportion of eligible patients were recruited for this study (term: 20 %; preterm: 44 %). Participation in this study was voluntary and parents were not required to give an explanation for declining. However, the few that did voluntarily provide an explanation indicated that they were

not keen for their baby to have venepuncture and other investigations that were not part of routine care. Some of the parents of term infants were unable to return to the hospital for the tests and scan. The number of term infants recruited was smaller than initially planned, thus reducing the power of our study.

We were unable to compare kidney growth in SGA and AGA premature babies. There were two deaths in our cohort, and both were SGA premature babies. The mortality rate among SGA premature babies is approximately 2.5–3 times greater than that of AGA premature babies [37]. The study was also limited in that we did not carry out weight measurements for premature babies and term babies using the same measuring scale. We used a weighing scale built into the neonatal incubator for measuring birth weight and then used an electronic weighing scale for subsequent measurements. We did not want to risk the development of hypothermia in the newborn premature babies, which is associated with increased mortality and morbidity [38]. We did not compare calibration between the incubators.

In conclusion, this study showed that premature babies have a smaller kidney volume and lower eGFR compared to term infants. We also demonstrated that eGFR has a good correlation with kidney volume, which supports the concept that kidney volume is a surrogate marker for nephron number in neonates. We propose that ex-premature infants should be followed-up prospectively with regular monitoring of renal growth, renal function, and blood pressure over their lifetimes.

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